METHODS FOR DIAGNOSING AND TREATING CANCERS

[0001] This application claims the benefit of U.S. Provisional Patent Application No. 62/989,164, filed Mar. 13, 2020, and U.S. Provisional Patent Application No. 63/000,187, filed Mar. 26, 2020, the entirety of which are incorporated herein by reference.

[0002] The invention was made with government support under Grant No. CA205965 awarded by the National Institutes of Health. The government has certain rights in the invention.

BACKGROUND OF THE INVENTION

1. Field of the Invention

[0003] The present invention relates generally to the field of molecular biology and medicine. More particularly, it concerns molecular biology and medicine.

2. Description of Related Art

[0004] Programmed death ligand-1 (PD-L1, CD274, B7-H1), a target of several FDA-approved cancer immunotherapies, is highly expressed on some cancers and enables immune evasion by inhibiting tumor-specific $CD8^+$ T cells (Topalian et al., 2012). The ability of expression of cell surface PD-L1 to predict responses to PD-1/PD-L1 antibodies in many cancers is not conclusive and has been controversial (Wang et al., 2016), suggesting that additional factor (s) other than tumor surface PD-L1 can affect such immunotherapy outcomes. Predictors of patient response to anti-PD-L1 or anti-PD-1 immunotherapy are not currently reliable. Patients with epithelial ovarian cancer typically have an extremely poor response to anti-PD-1 or anti-PD-L1 immunotherapy alone.

[0005] Cancers typically have genomic instability, and mutations in cancers are common. For example, genomic instability in cancer can arise from defects in the DNA damage response (DDR) that can increase mutation rate and/or chromosomal instability to drive cancer clonal evolution, tumor heterogeneity, and treatment resistance. DDR defects can nonetheless also create vulnerabilities in cancer cells, but not normal cells, that in some instances can be exploited in cancer therapies. For example, poly (ADP-ribose) polymerase (PARP) inhibitor (PARPi) monotherapy has been approved by the FDA to treat BRCA1-deficient cancers (Fong et al., 2009).

[0006] DDRi are antitumor agents that target DDR pathways or mediators of DNA replication and repair. DDRi include Chk1, Chk2, ATM, ATR, Wee 1, and DNA-PK (Pilie et al., 2018). Although several DDR inhibitors (DDRi) have been developed, predicting whether a cancer will respond to DDRi therapy is a significant clinical problem. There exists a significant clinical need to identify biomarkers that predict DDRi responses, apart from BRCA1 status, and to define DDRi resistance mechanisms.

[0007] Cancers continue to present a serious, often complex clinical problem that results in significant mortality. Clearly, there is a need for new and improved methods for treating cancers, personalizing cancer therapies, and identifying patients more likely to respond to specific anti-cancer therapies.

SUMMARY OF THE INVENTION

[0008] The present disclosure, in some aspects, overcomes limitations in the prior art by providing improved methods for treating cancers, including methods for personalizing cancer therapies and identifying cancers that may be sensitive or resistant to cancer therapies. In some aspects, it has been observed that tumor cytoplasmic PD-L1, and not surface-expressed PD-L1 (also referred to as "surface PD-L1"), predicts tumor responsiveness to therapies and patient survival. In some aspects, increased expression of any of the 5 LAMTOR proteins (referred to herein as "LAMTOR") was observed to be associated with poor prognosis and reduced survival in cancers. In some aspects, it has been observed that downstream signaling from tumor cytoplasmic PD-L1 (such as activation of mammalian target of rapamycin complex 1 [mTORC1]), can predict cancer treatment response. Additionally, in a variety of cancers, reductions in cytoplasmic PD-L1 expression have been observed to correlate with improved responsiveness to DDRi, such as inhibitors of Chk1 (Chk1i), ATM (ATMi) and/or inhibitors of PARP (PARPi). In some aspects, methods of predicting cancer treatment responses and patient prognosis based on expression of tumor cytoplasmic PD-L1, or the ratio of cytoplasmic PD-L1 to surface-expressed PD-L1, are also provided.

[0009] In some aspects, cytoplasmic PD-L1 or its downstream signaling effects have been observed to affect cancer prognosis and/or responsiveness to therapy. As shown in the below examples, using tumor cells engineered for subcellular-specific PD-L1 expression cytoplasmic, not surface-expressed, tumor PD-L1 activated mTORC1, inhibited anti-PD-L1 immune checkpoint blockade immunotherapy response, and altered tumor-infiltrating immune cells independent of tumor surface PD-L1 expression. These results were distinct from reported cytoplasmic PD-L1 tail signals and reported resistance mechanisms to immune checkpoint blockade (Wu et al., 2018). In tissues from 99 melanoma and 440 ovarian cancer patients, 20% of melanomas and ovarian carcinomas expressed predominantly cytoplasmic PD-L1 that predicted tumor mTORC1 activation and reduced survival, and 20% expressed predominantly surface PD-L1 that had no relationship to mTORC1 activation or survival. Using genetic manipulations of ovarian cancer and melanoma cell lines plus imaging, mass spectrometry, immunoprecipitation and bioinformatics tumor PD-L1 was observed to activate mTORC1 by affecting LAMTOR subunit messenger RNA content. Tumor Lamtor expression was observed to predicted survival in melanoma and ovarian cancer patients. An analysis of tumors obtained from a clinical trial of pembrolizumab, bevacizumab plus cyclophosphamide to treat patients with epithelial ovarian cancer revealed that tumor cytoplasmic PD-L1 predicted the clinical response of patients to the therapy, whereas surface-expressed PD-L1 and total tumor PD-L1 were uninformative for predicting clinical response. Considering that epithelial ovarian cancers typically do not respond to anti-PD-1 or anti-PD-L1 immunotherapy alone, such methods may be used, e.g., to identify patients with epithelial ovarian cancers can benefit from an anti-PD-1 or anti-PD-L1 immunotherapy.

[0010] As further shown in the below examples, reduced expression of PD-L1 in cancer cells was associated with increased sensitivity to DDRi in a variety of cancers. Cancer lines were genetically depleted of PD-L1 using either